

Environmental Protection Agency's
Methodology for Assessing Risk of
Exposure to Nasal Carcinogens

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Summary

The U.S. Environmental Protection Agency (EPA) has carried out risk assessments on a variety of chemicals that have been shown to induce nasal tumors in animals and/or humans. Human cancer potency estimates, however, were not always based on the induction of nasal tumors. For those that were, studies employing the inhalation route of exposure were used, with one exception. Extrapolation from the inhalation to the oral route has not been attempted for nasal carcinogens. A variety of uncertainties in assessing potency of nasal carcinogens is being addressed.

Keywords: risk assessment, methodology

Introduction

The EPA carries out risk assessment on potentially carcinogenic agents using recently developed risk assessment guidelines (EPA, 1987a). Since nasal carcinogens are evaluated with the aid of these guidelines, and since the methodology is similar irrespective of the target organ, these guidelines are briefly reviewed here. Chemicals assessed by EPA's Office of Health and Environmental Assessment (OHEA) for which there is some evidence of nasal tumor induction are then listed along with routes of exposure and the target organs used for cancer potency estimation. Finally, formaldehyde is discussed in more detail as an example of an EPA risk assessment for a nasal carcinogen.

EPA methods for assessing carcinogenic risk

Chemicals are selected for evaluation by determining (1) if the agent is present in the environment or proposed use will result in release into the environment, and (2) if the agent poses a potential carcinogenic hazard. The latter is determined by a review of physical-chemical properties, structure-activity relationships, metabolic and pharmacokinetic properties, toxicologic effects, and short-term and long-term tests.

A weight-of-evidence classification for potential carcinogenicity is then carried out. For agents considered to be either carcinogenic or potentially carcinogenic in humans, a potency estimate is made if adequate dose-response data are available. The EPA classification system for qualitatively assessing risk, which is an adaptation of the International Agency for Research on Cancer (IARC) approach, is summarized below.

When the weight of evidence for human studies is sufficient, indicating a causal relationship has been determined, the agent is classified as group A. These are considered to be known carcinogens.

When the weight of evidence for human studies is limited, indicating a causal relationship is credible, but other explanations such as chance, bias, or confounding cannot be adequately excluded, then the agent is classified as group B1.

When human evidence is inadequate or lacking and sufficient evidence of carcinogenicity in animals is available as shown by an increased incidence of malignant tumors or benign and malignant tumors combined: (a) in multiple species or strains; (b) in multiple experiments; or (c) to an unusual degree in a single experiment, then the agent is classified as group B2. Chemicals classified as either category B1 or B2 are considered to be probable human carcinogens.

When human evidence is inadequate or lacking and evidence for carcinogenicity in animals is limited due to a lack of more than one study, inadequate dosage levels, inadequate duration of exposure, etc., the agent is classified as group C. These are considered to be possible human carcinogens.

When human evidence is inadequate or lacking and animal evidence is also inadequate or lacking, the agent is classified as group D.

When there is evidence for noncarcinogenicity as shown by a lack of association between exposure and cancer in well-designed animal studies and either no data or evidence for noncarcinogenicity in human studies, the agent is classified as category E.

Agents that are judged to be in category A or B are regarded as suitable for quantitative risk assessments. Agents classified as group C are generally suitable for quantitative risk assessment, but judgments must be made on a case-by-case basis. Human epidemiologic studies are preferred if adequate exposure data exist. In the absence of appropriate human studies, data from animals responding most similarly to humans are used. If it is uncertain which species responds to the agent in question most similarly to humans, the most sensitive responding species is used because the human is considered to be as sensitive as the most responsive species.

Benign and malignant tumors are combined for risk estimation unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin. Tumor sites with statistically significant elevations are usually pooled for estimation of total risk. Risk estimates, however, may also be carried out for individual tumor sites or types to determine risk for that site.

When the exposure route in the species from which the dose-response information is obtained differs from the route occurring in environmental exposures, route extrapolation may be carried out if it is feasible based upon metabolic and pharmacokinetic considerations. All assumptions regarding the extrapolation must be presented along with a consideration of uncertainties.

In the absence of adequate information to the contrary, mathematical extrapolation to low doses is carried out using a linearized multistage procedure. When pharmacokinetic or metabolic data or other substantial evidence on the mechanistic aspects of carcinogenesis exists, a low-dose extrapolation model, other than the linearized multistage procedure, might be more appropriate on biologic grounds. If adequate data exist, a time-to-tumor model may be used.

In the absence of comparative toxicologic, physiologic, and pharmacokinetic data for a given suspect carcinogen, the EPA takes the position that species extrapolation of effective dose on the basis of body surface area is most appropriate.

Nasal carcinogens assessed by OHEA

Evidence for induction of nasal tumors has been shown for 26 of the chemicals assessed by OHEA. Cancer potency, however, either was not estimated, or was based on other tumor sites or a combination of tumor sites for 17 of these chemicals. These 17 include acrylonitrile, benzo(a)pyrene, 1,2-dibromomethane, 1,2-dichloro-2-butene, dimethylsulfate, 2,3,7,8-tetrachlorodibenzo-p-dioxin, 1,1-dimethylhydrazine, nickel, n-nitrosodiethanolamine, n-nitrosodiethylamine, n-nitroso-n-propylamine, n-nitrosodimethylamine, n-nitrosomethylvinylamine, n-nitrosopiperidine, n-nitrosopyrrolidine, phenacetin, and vinyl chloride. Nasal tumors were not used for potency determination because the study selected was of better quality than the one inducing nasal tumors, other sites appeared to be more sensitive to tumor induction, or the route of exposure by which nasal tumors were induced was not considered to be appropriate for human exposure.

Data were considered to be inadequate for potency estimation in four of the chemicals. The study selected for potency estimation used the oral route of exposure (gavage, drinking water, or food) for 10 of the chemicals and inhalation for the other three. Liver and stomach tumors were used to estimate potency for most of the chemicals, although tumors of the brain, bladder, and lungs were selected for acrylonitrile, nickel, and phenacetin, respectively. While inhalation is considered to be the usual route of exposure for induction of nasal tumors, they were induced by other routes in six of these 17 chemicals.

It should be pointed out that the EPA does not assume site concordance for cancer when extrapolating from animals to humans. Thus, although nasal tumors were not used for cancer potency estimates in any of these chemicals, this does not rule out the possibility, or even the likelihood, that the nasal region may be the critical site for tumor induction in humans.

Chemicals for which OHEA has estimated carcinogenic potency based on nasal tumor induction are listed in Table I. While adequate animal evidence was available for all of these chemicals, human evidence was considered to be adequate only for bis(chloromethyl)ether and limited for formaldehyde. The potency values for nasal tumor induction were all based on animal studies since human exposure data were inadequate for the two chemicals classified in categories A and B1. Additional potency estimates were developed using other tumor sites for three of these chemicals; kidney, liver, and stomach tumors induced via the diet for 1,2-dibromo-3-chloropropane; liver tumors induced via gavage for epichlorohydrin; and stomach tumors induced via drinking water for hydrazine.

All of the potency determinations for the nasal carcinogens listed in Table I, except one, were derived on the basis of air concentrations using inhalation exposure studies. The only exception was 1,4-dioxane where the potency was estimated for oral intake only. It was converted to an equivalent air concentration, assuming that route extrapolation is valid, only to compare it with the other values listed in Table I.

There is no direct proof as to why the nasal region is the critical target site for oral exposure to 1,4-dioxane. The nasal region is not uniquely susceptible since tumors can also be induced at other sites (NCI, 1978). The high vapor pressure of this chemical, however, suggests that exposure occurs by exhalation through the lungs. If this is true, in order to accurately extrapolate a drinking water dose to an inhaled concentration, it would be necessary to determine the relationship between the ingested dose and concentration in the nasal passages.

Table I. Chemicals assessed by the EPA for which the cancer potency is based on induction of nasal tumors.

Chemical	q_1^*	Category	Reference
Acetaldehyde	2.2×10^{-6}	B2	Woutersen et al., 1984
Bis(chloromethyl)ether	2.7	A	Kuschner et al., 1975
1,2-Dibromo-3-chloropropane	2.4×10^{-3}	B2	Reznik et al., 1980
Dimethylcarbamoylchloride	1.9×10^{-2}	B2	Sellakumar et al., 1980
1,4-Dioxane	2.3×10^{-6}	B2	Hoch-Legeti et al., 1970
Epichlorohydrin	1.3×10^{-6}	B2	Laskin et al., 1980
Formaldehyde	1.3×10^{-5}	B1	Kerns et al., 1983
Hydrazine	4.9×10^{-3}	B2	MacEwen et al., 1981
Propylene oxide	3.7×10^{-6}	B2	NTP, 1985

The q_1^* represents the 95 percent upper-bound risk estimate for lifetime exposure to 1 ug/m^3 .

Inhalation of 1,4-dioxane volatilizing from the treated water could further complicate dosimetry.

Formaldehyde can be taken as an example of a chemical recently assessed by the EPA (1987b). To determine the weight of evidence for carcinogenicity in humans, 28 epidemiologic studies were evaluated. In the three studies that were adequate in design to detect small to moderate risks associated with formaldehyde exposure, there was a statistically significant association between respiratory cancer and formaldehyde exposure. Because of confounding factors, especially exposure to other agents, the human evidence was considered to be limited. Nasal cancer was also induced in several animal studies, including that by Kerns et al. (1983). Based on the available evidence, formaldehyde best fit category B1, a probable human carcinogen.

Since adequate exposure data were not available for humans, the animal exposure study by Kerns et al. (1983), in which rats were exposed to 2, 5.6, and 14.3 ppm for 24 months, was used to estimate potency. The data were adjusted for interim sacrifices and early deaths. Parts per million were considered to be equivalent between humans and experimental animals. This assumes that respiration varies directly with metabolic rate. While respiration has been shown to be slightly inhibited in rats breathing high concentrations of formaldehyde, an adjustment would result in only a minor change in the potency estimate.

Since risk at low exposure cannot be measured directly by either animal or human epidemiologic studies, a number of low-dose extrapolation models were developed. Preliminary risk estimates were calculated based on 11 of these models using data from the Kerns et al. (1983) study. When information is limited, models incorporating linearity are recommended by the EPA guidelines. Since formaldehyde is known to be mutagenic, is structurally related to other carcinogens, is cytotoxic, and is clearly carcinogenic in the rat, the linearized multistage model, without restrictions on the order of the polynomial, is the model of choice. The recommended q_1^* value of 1.3×10^{-5} was derived using this model.

The argument can be made that there is a dose level below which the added risk of cancer from exposure to formaldehyde is zero. There is, however, no consensus in the scientific community on this topic.

Additionally, there is no way, through the use of mathematical models, to demonstrate either the existence or nonexistence of a threshold. If thresholds exist, they are likely to vary among members of the population at risk and may be modified by other environmental agents. Therefore, use of a dose-response model incorporating a single threshold would provide an estimate of average population threshold that would have little utility. Thus, it is assumed that there is no threshold.

Dosimetric considerations

A variety of errors is possible when extrapolating risk from animals to humans. Some of these errors, such as differences in metabolic pathways and target organ sensitivity, are common to any species extrapolation. Others are more specific to nasal tumor induction. For example, the surface area of the nasal passages will often differ among species; the efficiency of deposition, especially for inhaled particulate matter, can differ; clearance rates can vary, allowing for differing degrees of particle solubilization and thereby bioavailability; and finally, high experimental concentrations may result in an inhibition of respiration (Chang et al., 1981).

Unfortunately, adjustments to account for such factors are limited by lack of adequate data as well as sophisticated methodology. In order to improve dosimetry estimates for inhaled chemicals, the EPA is currently developing appropriate methodology which will be published as inhalation reference dose guidelines. The availability of adequate data, however, will still limit the application of these guidelines.

As noted previously, some chemicals have been shown to induce nasal cancer by routes other than inhalation. While not having done so yet, it is likely that the EPA will be called upon to carry out route extrapolation for cancer potency of nasal carcinogens in the future. In order to do so it will be necessary to account for several factors including volatility of the parent compound, solubility, bioaccumulation at the target site, as well as requirements for metabolic activation.

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